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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,488	02/16/2000	MAURICE MOLONEY	9369-98	6010

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/402,488	Applicant(s) MOLONEY ET AL.	
	Examiner David J Steadman	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,12-16,18-20,24-30,41,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,13-16,19,20,24-26,28-30,41,43 and 44* is/are rejected.

7)☒ Claim(s) *12,18 and 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

[1] Claims 1, 4-10, 12-16, 18-20, 24-30, 41, 43, and 44 are pending in the application.

[2] Applicant's amendment to the specification, cancellation of claims 11, 17, 31-40, and 42, amendment to claims 4, 5, 7-10, 12-14, 18-20, 24-28, 41, 43, and 44 in Paper No. 27, filed August 04, 2003, is acknowledged.

[3] It is noted that claims 45-47 were pending prior to the instant amendment of Paper No. 27. While these claims have been canceled by the amendment of Paper No. 27, the amendment of Paper No. 27 provides no indication that claims 45-47 are to be canceled. If applicant intends for these claims to remain pending, it is suggested that applicant include these claims re-numbered as claims 48-50 in a subsequent amendment.

[4] It is further noted that applicant has cited the reference of Nomura et al. (*Biosci Biotech Biochem* 59:382-387) in response to the rejection under 35 USC 103(a) (see page 11 of Paper No. 27) without supplying this reference for the examiner's review. It is suggested that in future responses applicant provide the examiner with a copy of cited references not of record such that the examiner can expeditiously respond to applicant's arguments.

[5] Applicant's arguments filed in Paper No. 27 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

[7] Claim 12 is objected to in the recitation of "milk, , the". It is suggested that "milk, , the" be replaced with "milk, the". Appropriate correction is required.

[8] Claims 18 and 27 are objected to as being dependent upon a rejected base claim but otherwise appear to be in a condition for allowance.

Claim Rejections - 35 USC § 112, Second Paragraph

[9] The rejection of claim 8 under 35 USC 112, second paragraph, is maintained for the reasons of record and the reasons stated below. Applicant argues the claim has been amended as suggested by the examiner. Applicant's argument is not found persuasive as the amendment as suggested by the examiner has not been applied to claim 8.

Claim Rejections - 35 USC § 102

[10] The rejection of claims 20, 25, 26, 28-30, 41, 43, and 44 under 35 USC 102(b) as being anticipated by Hiramatsu et al. (*Appl Environ Microbiol* 56:2125-2132, 1990) is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 14 of Paper No. 26). Applicant argues (beginning at page 9 of Paper No. 27) Hiramatsu et al. (1990) teach one vector, JGH2, that contains only five amino acids out of forty total amino acids of a chymosin pro-peptide. Applicant argues that one of ordinary skill in the art would not interpret an amino acid sequence comprising only five N-terminal residues of a chymosin pro-peptide as "a chymosin pro-peptide" as recited in the claims and thus, the claims are not anticipated by Hiramatsu et al. (1990). Applicant's argument is not found persuasive.

It is the examiner's position that, based on the definition provided in the specification of the term "pro-peptide", an ordinarily skilled artisan would recognize that even as few as five amino acids of a chymosin pro-peptide can be a "chymosin pro-peptide" as recited in the claims. MPEP § 2111 directs the examiner to give claims "their broadest reasonable interpretation consistent with the specification". In the present case, the term rennin is synonymous with chymosin and the term "pro-peptide" is defined in the specification as, "the amino terminal portion of a zymogen or a functional portion thereof up to the maturation site" (page 5, lines 24-25 of the specification). This definition does not limit the "pro-peptide"

as recited in the claims to a full length pro-peptide. As the five amino acids of an MPR pro-peptide as encoded by vector JGH2 satisfy the definition of "pro-peptide" as defined in the specification, one of ordinary skill in the art would recognize that the five amino acids of an MPR pro-peptide as encoded by vector JGH2 are "a chymosin pro-peptide" as recited in the claims.

Claim Rejections - 35 USC § 103

[11] The rejection of claims 1, 4, 6-10, 13-16, and 19 are under 35 U.S.C. 103(a) as being unpatentable over Hiramatsu et al. (1990) in view of Hiramatsu et al. (*J Biol Chem* 264:16862-16866, 1989) is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 15 of Paper No. 26). Applicant argues (beginning at page 10 of Paper No. 27) Hiramatsu et al. (1990) report they did not get efficient cleavage of the pro-sequence from the human growth hormone (hGH) polypeptide and suggest introducing an artificial cleavage site between the pro-peptide sequence and the hGH polypeptide sequence. Applicant argues the suggestion by Hiramatsu et al. (1990) to introduce an artificial cleavage site teaches away from the claimed invention. Applicant's argument is not found persuasive.

Hiramatsu et al. (1990) teach the removal of the extra amino acids of the MPR pro-peptide is required to obtain hGH with the same amino terminus as native hGH (page 2131, left column, bottom). Hiramatsu et al. (1990) suggest incorporating an artificial factor Xa cleavage site in order to cleave the pro-peptide sequence (page 2131, left column, bottom). However, incorporating an artificial factor Xa cleavage site in order to cleave the pro-peptide sequence is clearly a suggestion and in no way teaches away from the claimed invention. In fact, Hiramatsu et al. (1990) provide the motivation for using the full length MPR pro-peptide fused to hGH as rendered obvious by the combined references. As stated in a previous Office action, including the full-length MPR pro-peptide to a full length polypeptide (as demonstrated by Hiramatsu et al. (1989)) would provide a means for obtaining hGH with the same amino

terminus as native hGH by cleavage with endogenous yeast proteases without need for incorporating an artificial factor Xa cleavage site, which would require the addition of factor Xa for cleavage.

Applicant argues (beginning at the bottom of page 10 of Paper No. 27) the deficiencies of Hiramatsu et al. (1990) are not remedied by Hiramatsu et al. (1989) as Hiramatsu et al. (1989) is not concerned with the preparation of heterologous proteins and instead teaches expression of pre-pro-MPR and autocatalytic processing to cleave the pre- and pro-peptides by endogenous yeast proteases. Applicant's argument is not found persuasive.

While neither of the cited references alone teaches the claimed invention, the combination of references makes obvious a nucleic acid encoding an MPR pro-peptide fused directly to hGH and a method for producing a recombinant protein using said nucleic acid. While Hiramatsu et al. (1989) do not teach expression of an MPR pre-pro-peptide fused to a *heterologous* protein, i.e., a non-MPR protein, Hiramatsu et al. (1989) nonetheless provide evidence that a pre-pro-peptide fused to a polypeptide is cleaved from the polypeptide using endogenous yeast proteases, without need for adding factor Xa, or some other protease for cleavage of the pro-peptide.

At the middle of page 11 of Paper No. 27 applicant argues that if it would have been obvious to one of ordinary skill in the art to combine the cited references to teach replacement of the pro-peptide fragment with a full length MPR pro-peptide, then it would have been discussed in the conclusion of Hiramatsu et al. (1990). Applicant reiterates their argument that the suggestion by Hiramatsu et al. (1990) to introduce an artificial cleavage site teaches away from the claimed invention. Applicant argues that even if an ordinarily skilled artisan were motivated to use the full length MPR pro-peptide, there would be no guarantee of success of efficient cleavage. Applicant's argument is not found persuasive.

In no way do the teachings of Hiramatsu et al. (1990) teach away from the claimed invention. Addressing applicant's argument that Hiramatsu et al. (1990) would have discussed using a full length MPR pro-peptide, without expressly addressing the authors of the manuscript as to why such a discussion was not included in their manuscript, there is no way to know why Hiramatsu et al. (1990) do not address using a full length MPR pro-peptide and the examiner chooses not to speculate as to why such a

discussion is not included. Hiramatsu et al. (1990) teach the necessity of cleaving the MPR pro-peptide portion from the hGH and provide, as a suggestion, incorporating an artificial factor Xa cleavage site in order to cleave the pro-peptide sequence (page 2131, left column, bottom). Based on the combined teachings of Hiramatsu et al. (1990) and Hiramatsu et al. (1989), one of ordinary skill in the art would have had a *reasonable expectation* of success for making the claimed invention. A "guarantee of success" as argued by applicant is not required. Obviousness does *not* require absolute predictability of success (*In re O'Farrell* (CAFC) 7 USPQ2d 1673 (8/10/1988)) and, at the time of the invention, in view of the combination of cited references and the state of the art, an ordinarily skilled artisan would have had a *reasonable* expectation of success for making the claimed invention.

Applicant argues (page 11 of Paper No. 27) the inventiveness of the claimed invention is supported by Nomura et al. (*Biosci Biotech Biochem* 59:382-387) who teach the entire MPR gene is needed for efficient secretion of the heterologous protein apolipoprotein E (ApoE). Applicant argues that at the time of the invention one of skill in the art would not predict that the method of the instant invention, where only a pro-peptide is used, would be efficient for the production and cleavage of a heterologous protein. Applicant's argument is not found persuasive.

Nomura et al. teach "the prepro-region (-61 Met to –1 Phe) was shown to be useful for secretion of human growth hormone and urokinase by *S cerevisiae*" (page 383 right column, bottom to page 384, left column, top). Nomura et al. teach using a similar strategy for expression and secretion of human ApoE failed to result in any detectable level of protein (page 384, left column, bottom to right column, top) and explain this result as being due to the rapid degradation of the human ApoE protein by yeast proteases (page 382, abstract and page 386, right column, bottom). The result obtained using only the prepro-region of MPR fused to human ApoE appears to be specific to human ApoE as this result was not obtained using either of hGH or urokinase as taught by Nomura et al. as stated above. Based on the teachings of Nomura et al., one of ordinary skill in the art would not attempt to express human ApoE using the system that was used for successfully expressing and secreting hGH and urokinase, particularly as Nomura et al. teach, "[human ApoE] seems to be difficult to secrete from yeast cells" (page 384, right

column, bottom). Because hGH and urokinase were successfully expressed and secreted by yeast, one of ordinary skill in the art would recognize that including a full length MPR pro-peptide fused to hGH would allow successful expression and secretion of the fusion protein with subsequent cleavage of the pro-peptide from the hGH component due to endogenous yeast proteases. The evidence provided by Nomura et al. fails to demonstrate objective evidence to show nonobviousness and based on the teachings of the combined references, the claimed invention would have been obvious to one of ordinary skill in the art at the time of the invention.

[12] The rejection of claim 5 under 35 U.S.C. 103(a) as being unpatentable over Hiramatsu et al. (1990) in view of Hiramatsu et al. (*J Biol Chem* 264:16862-16866, 1989) as applied to claims 1, 4, 6-10, 13-16, and 19 above and further in view of Fine et al. (*Gen Comp Endocrinol* 89:51-61) and the rejection of claim 24 as being unpatentable over Hiramatsu et al. (1990) in view of Fine et al. are maintained for the reasons of record and the reasons stated below. The rejections were fully explained in a previous Office action (see items 16 and 17 of Paper No. 26). Applicant argues (beginning at the bottom of page 11 of Paper No. 27) claims 5 and 24 relate to a specific embodiment wherein the heterologous protein is carp growth hormone (cGH). Applicant argues the deficiencies in the Hiramatsu et al. (1990) and Hiramatsu et al. (1989) references are not remedied by Fine et al., a reference which teaches expression of cGH in *E. coli.* Applicant argues the reference of Fine et al. in no way teaches or suggests to link a pro-peptide to a heterologous protein and since applicant is claiming a method for production of cGH by a novel method or in a novel nucleic acid construct, the claims are patentable over the cited references. Applicant's argument is not found persuasive.

It is the examiner's position that the combined references of Hiramatsu et al. (1990) and Fine et al. or Hiramatsu et al. (1990), Hiramatsu et al. (1989), and Fine et al. render the claimed invention obvious. While the reference of Fine et al. shows expression of cGH using *E. coli*, there is no reason to expect that expression of cGH would not also occur in yeast as Hiramatsu et al. (1990) demonstrate successful expression of the human homologue of cGH in yeast. Furthermore, applicant has presented no evidence to indicate or suggest that cGH would not be successfully expressed in yeast. While the

reference of Fine et al. alone does not teach the claimed invention, it is the combination of references that renders the claimed invention obvious. Fine et al. discuss the pharamocologic use of cGH as a growth promoting tool (page 51, right column) and the advantages of producing a eukaryotic protein in a eukaryotic host as opposed to a prokaryotic host (such as E. coli) were well known in the art at the time of the invention. Thus, one would have been motivated to make an expression construct encoding an MPR prepro-region fused to cGH for expression in a yeast. Based on the teachings of Hiramatsu et al. (1990) and Fine et al. references, one of ordinary skill in the art would have recognized a reasonable expectation of success that the fusion protein expressed and secreted would have been cleaved into the pro-peptide and cGH components using endogenous yeast proteases. Thus, claims 5 and 24 are obvious in view of the cited references.

Conclusion

[13] Status of the claims:

- Claims 1, 4-10, 12-16, 18-20, 24-30, 41, 43, and 44 are pending.
- Claims 1, 4-10, 13-16, 19, 20, 24-26, 28-30, 41, 43, and 44 are rejected.
- Claims 12, 18, and 27 are objected to.
- No claim is in condition for allowance.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or

relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman
Patent Examiner
Art Unit 1652

REBECCA E. PRUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600